Neoadjuvant chemotherapy with low dose of pegylated liposomal doxorubicin plus weekly paclitaxel in operable and locally advanced breast cancer

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To determine the activity and safety of a schedule with a low dose of pegylated liposomal doxorubicin (PLD) and weekly paclitaxel in operable and locally advanced breast cancer patients. Thirty-five patients with histologically confirmed, operable, and locally advanced breast cancer entered the study. The median age was 59 years (range 31–74 years). The schedule was biweekly PLD at the dose of 15 mg/m^2 for four administrations and weekly paclitaxel at the dose of 80 mg/m^2 for eight administrations. All patients were evaluable for response and toxicity. Twenty-six patients responded (74%): three (8%) had a complete response and 23 (66%) had a partial response, seven (23%) remained stable, and one experienced progression (3%). Fifteen of 27 operable patients (55%) underwent conservative surgery. Three patients (9%) had a pathological complete response and the disappearance of infiltrating disease was documented in three other patients. The main toxicity was hand–foot syndrome (grade 3 in four patients; 11%). Other nonhematological grade 3 toxicities included stomatitis in three patients (8%) and liver toxicity in one patient (3%). Grade 3–4 neutropenia was documented in another three patients and dose reduction was necessary in two patients. The fourth administration of PLD was suspended in four patients for grade 2–3 hand–foot syndrome. No symptoms were related to impairment of cardiac function and no death related to toxicity occurred. The combination of biweekly PLD and weekly paclitaxel was active in operable and locally advanced breast cancer with a manageable safety profile. *Anti-Cancer Drugs* **19:733–737 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Conventional doxorubicin played an important role in the treatment of breast cancer patients and remains a mainstay of therapy in adjuvant and neoadjuvant settings [1,2]. Unfortunately, its clinical utility is limited by a poor toxicity profile with acute (nausea, vomiting, stomatitis, myelosuppression, alopecia) and chronic side effects (cardiotoxicity) [3,4]. The combination of doxorubicin and paclitaxel is widely used in advanced disease [5] and has demonstrated its efficacy when shifted toward a preoperative setting [6]. However, this schedule presented high cardiac risk [7], myelosuppression, infectious complications and mucositis, which made its routine use in clinical practice problematic [8]. Encapsulation of doxorubicin into liposomes coated with methoxy-polyethyleneglycol favorably improves the toxicity profile of the active agent and produces prolonged circulation, modifying the pattern of drug distribution [9,10]. In the first phase II trial of pegylated liposomal doxorubicin (PLD) in metastatic breast cancer, a response rate of 31% was obtained with 16 partial and four complete responses in 64 evaluable patients; the main toxicity was hand–foot syndrome, especially in patients treated with a dose of 60 mg/m^2 (hand–foot syndrome was less frequent with a dose of 45 mg/m^2) [11]. On the other hand, there was accumulating evidence that favored a dose of paclitaxel delivered weekly versus every 3 weeks [12]. A phase II study by Schwonzen *et al.* [13] in pretreated metastatic breast cancer patients with PLD (20 mg/m^2, day 1) and paclitaxel (100 mg/m^2, days 1 and 8) for six cycles every 2 weeks, documented 48% of the response rate. However, this schedule reported severe side effects: grade 3 nonhematological toxicity (hand–foot syndrome 29%, neuropathy 24%, mucositis 13%) and grade 4 leukopenia (48%); the authors recommended 15 mg/m^2 PLD every 2 weeks and 80 mg/m^2 weekly paclitaxel. A further phase I study by Androulakis *et al.* [14] in patients with advanced solid tumors recommended the weekly dose of 10 mg/m^2 PLD and 80 mg/m^2 paclitaxel for four consecutive weeks, every 6 weeks. Other phase I studies explored maximum tolerated dose of similar schedules with escalating doses of PLD from 12.5 to 22.5 mg/m^2 every 2 weeks and

0959-4973

paclitaxel 80 mg/m^2/week or 90–115 mg/m^2 every 2 weeks [15,16]. The activity of the PLD and paclitaxel combination as neodjuvant treatment was documented in a phase II study by Gogas *et al.* [17]; 35 patients with locally advanced breast cancer were treated with PLD (35 mg/m^2) and paclitaxel (175 mg/m^2), every 3 weeks for four to six cycles, with a clinical response rate of 74% and a pathological complete response in three patients (8%). Toxicity was mild with grade 3 hand–foot syndrome in three patients (9%), grade 3 skin toxicity in four patients (11%), and grade 3–4 neutropenia in 15% of patients. However, no study has been performed to test the activity of other PLD and paclitaxel schedules on patients unsuitable for conservative surgery. On these bases we decided to plan a phase II study in operable and locally advanced breast cancer to determine activity, safety, and percentage of conservative surgery delivering a lower dose of PLD with weekly paclitaxel.

Patients and methods

Eligibility criteria

Thirty-five patients with histologically confirmed breast cancer entered the study. Patients with tumor size, mammographically detected, larger than 2 cm – with or without axillary palpable lymph nodes – were enrolled. The study included patients with operable disease but not candidates – particularly for breast size – for conservative surgery at the time of diagnosis (T2 N0; T2–3 N0–1; T2–3 N1–2) and patients with locally advanced breast cancer (T4a,b,c, N0-3; T4d); a fine needle aspiration was not performed in patients with palpable axillary lymph nodes. After mammography and core needle biopsy, all patients underwent staging with a complete blood count, chemistry profile, chest radiograph, liver ultrasound, and bone scan. Other selection criteria included (a) age of 18 years or more; (b) ECOG performance status 0–1; (c) adequate renal, liver, and bone marrow function; and (d) a life expectancy of at least 12 months.

Exclusion criteria included (a) coexistent diagnosis of ischemic cardiopathy or other cardiopathy (an evaluation of left ventricular ejection with ultrasound or MUGA scan was not performed in asymptomatic patients before neoadjuvant and adjuvant chemotherapy); (b) previous treatment for breast cancer, including surgery, radiation, cytotoxic, and endocrine treatment; (c) previous cancer except for curatively treated nonmelanoma skin cancer or carcinoma *in situ* of the cervix; (d) peripheral neuropathy; and (e) active infection or other serious medical or psychiatric condition, which would impair the ability of the patient to receive protocol treatment.

The primary objective was to access the efficacy of low dose of PLD every 2 weeks with weekly paclitaxel in locally advanced and operable breast cancer; secondary objectives were the evaluation of safety and the rate of a conservative surgical approach. Written informed consent was obtained from all patients.

Study design

The schedule consisted of PLD (15 mg/m^2) every 2 weeks (for four administrations) and paclitaxel (80 mg/m^2) every week (for eight administrations).

After the completion of preoperative chemotherapy, all patients underwent mammography; the objective response was evaluated on breast tumor according to World Health Organization criteria [18]. Patients with complete or partial response of breast tumor were evaluated for conservative surgery, except for patients with T4a, b, c, d (thus, the percentage of breast-conserving surgery has been evaluated only in operable patients). Responding patients were treated with adjuvant chemotherapy consisting of doxorubicin/cyclophosphamide, doxorubicin/cyclophosphamide followed by paclitaxel, epirubicin and paclitaxel (concomitant or sequential); docetaxel-based chemotherapy was administered to other patients. The schedules administered were AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) for four cycles; AC for four cycles followed by paclitaxel (175 mg/m^2) for four cycles; epirubicin (90 mg/m^2) plus paclitaxel (175 mg/m^2) for four to six cycles; epirubicin (100 mg/m^2) for four cycles followed by paclitaxel (175 mg/m^2) for four cycles; docetaxel (100 mg/m^2) for six cycles; and TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2; cyclophosphamide 500 mg/m^2) for six cycles. After adjuvant chemotherapy, premenopausal patients with hormone-receptor positive, started hormonal therapy with tamoxifen (20 mg/day for 5 years) and LH–RH analogous (for 2 years); postmenopausal patients started an aromatase inhibitor for 5 years. Patients with conservative surgery and those with baseline T4 tumor were considered for radiotherapy on residual breast or chest wall, respectively. Surgical specimens were evaluated for a pathological response on breast and axillary lymph nodes. The disappearance of tumor cells was considered as a pathological complete response.

Dose reduction

A blood count and chemistry profile were performed the day before chemotherapy. In the case of grade 3 and 4 neutropenia or thrombocytopenia, treatment was delayed until the absolute neutrophil count was $\geq 1500/mm^3$ and platelets count was $\geq 100\,000/mm^3$ (for patients with grade 4 neutropenia, G-CSF administration was permitted for at least 3 days or until complete neutrophil recovery, at the dose of 30 μg every day subcutaneously). In the case of grade 4 hematological toxicity, the dose of PLD and paclitaxel was reduced by 25% in subsequent cycles. In the case of grade 3 hand–foot syndrome, administration of PLD was temporarily interrupted; if the hand–foot syndrome did not improve to a grade 1 or 2 in

the subsequent cycle, PLD was permanently interrupted and the patient was off study. The dose of PLD and paclitaxel could be reduced by 25% for any grade 3 nonhematological toxicity; treatment was permanently interrupted for any grade 4 nonhematological toxicity. Toxicity was evaluated according to NCI-CTC criteria.

Statistical design

The sample size was based on the objective response on breast tumor evaluated with mammography after the completion of preoperative chemotherapy. According to Simon's two-stage minimax design, for a target activity level of at least 70% (p1–p0 = 0.20), 13 responses had to be documented in the first 18 evaluable patients (α error = 0.05; β error = 0.10). In this case the accrual had to be continued to 32 patients. The schedule was considered active if 26 responses occurred in the 32 evaluable patients.

Results

Patients' characteristics are listed in Table 1. All patients were evaluable for response and toxicity; 28 patients completed the planned treatment and 34 patients underwent surgery (one patient refused surgical intervention). Objective responses were documented in 26 patients (74%) [95% confidence interval 63.23–91.05%]; three complete (8%) and 23 partial (66%) responses. The disease was stable in eight patients (23%) and progressed in one patient (3%). Fifteen of 27 operable patients (55%) underwent a conservative surgery and a quadrantectomy was performed. A pathological complete response on breast and axilla was documented in three patients (9%) and a pathological complete response on axilla was reported in another six patients (18%; five IIIA patients and one IIIB patient at the baseline stage). The disappearance of infiltrating disease has been shown in three other patients (9%). See Table 2. The safety profile of the schedule is listed in Table 3. The main toxicity was hand–foot syndrome: grade 3 in four patients (11%) and grade 2 in nine patients (26%). After five episodes of grade 2–3 hand–foot syndrome in the first 15 patients, we decided to consider the prophylactic use of pyridoxine [19]. Therefore, in the following 20 patients we administered oral pyridoxine (300 mg) once a day from day 1 to day 56 of chemotherapy. In the group without pyridoxine, one grade 3 and four grade 2 hand–foot syndromes were documented (33%); in the group with pyiridoxine, three grade 3 and five grade 2 hand–foot syndromes were observed (40%). Other nonhematological grade 3 toxicities included stomatitis in three patients (8%) and transaminase increase in one patient (3%). Hematological toxicity was very low with grade 3 neutropenia in two patients (6%) and grade 4 in one patient (3%). No episode of thrombocytopenia was reported. Dose reduction by 25% was necessary only for two patients because of grade 3–4 neutropenia (with G-CSF administration); a third patient underwent G-CSF administration for grade 2 neutropenia with a protocol violation. The fourth course of PLD was interrupted in four patients for grade 3 hand–foot syndrome. Two patients dropped out the study after three courses of PLD and six courses of paclitaxel: one patient for grade 3 hand–foot syndrome associated with grade 3 stomatitis (that did not improve after 2 weeks of rest) and one patient for informed consent withdraw. In another patient, we decided to stop chemotherapy after three courses of PLD and five courses of paclitaxel because of clinical worsening of leg psoriasis with additional skin infection. No symptoms related to impairment of cardiac function were reported. No death related to toxicity occurred. To date, all patients are still alive; one patient progressed to mediastinal lymph nodes, one patient

Table 1 Patients' characteristics

No. of patients	35
Age (median)	59 (range, 31–74)
Baseline stage	
IIA	5 (14%)
IIB	2 (6%)
IIIA	20 (57%)
IIIB	8 (23%)
Menopausal status	
Pre	15 (43%)
Post	20 (57%)
Estrogen receptor	
Positive	26
Negative	8
Unknown	1
HER-2 status (Hercept test)	
0	14
1+	9
2+	4[a]
3+	7
Unknown	1

[a]Fluorescence in-situ hybridization not amplified.

Table 2 Response

	No. of patients	%
Complete response	3	8
Partial response	23	66
Stable disease	8	23
Progressive disease	1	3
Conservative surgery	15	55
Pathological complete response on breast and axilla	3	9[a]
Pathological complete response on axilla	6	18
Intraductal carcinoma	3	9

[a]One patient refused surgery; three of 34 patients are evaluable for pathological response.

Table 3 Toxicity

	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hand–foot syndrome	9 (26)	4 (11)	0
Stomatitis	4 (11)	3 (8)	0
Vomiting	1 (3)	0	0
Diarrhea	1 (3)	0	0
Skin rush	3 (8)	0	0
Neutropenia	2 (6)	2 (6)	1 (3)
Hepatotoxicity	2 (6)	1 (3)	0
Sensorial neuropathy	1 (3)	0	0
Arthralgia/myalgia	3 (8)	0	0

presented a second tumor on contralateral breast, and one patient progressed to the bones.

Discussion

Anthracyclines and taxane are the reference drugs for neoadjuvant chemotherapy in the treatment of breast cancer and their combination has been tested in a number of phases II and III studies. Complete clinical responses ranged from 9 to 34% and pathological complete responses varied from 5 to 27.5% in all patients [20]. In a phase II study by Moliterni *et al.* [21], a schedule with doxorubicin (60 mg/m^2) rubicin and paclitaxel (200 mg/m^2) was administered in locally advanced breast cancer patients: clinical complete response was documented in 31% of patients. In phase III study by Dieras *et al.* [6], 200 patients with T2–3, N0–1, M0 disease were randomized to receive doxorubicin (60 mg/m^2) plus paclitaxel (200 mg/m^2) or cyclophosphamide (600 mg/m^2), every 3 weeks for four cycles; objective clinical response was 89% in the doxo rubicin/paclitaxel arm and 70% in the doxo rubicin/cyclophosphamide arm with a pathological complete response in 16 and 10% of patients, respectively. Unfortunately, these active schedules have a poor toxicity profile with a high risk of myelosuppression, mucositis, neurotoxicity, and cardiotoxicity. To overcome some of these side effects, a liposomal doxorubicin has been developed: pegylated liposomal doxorubicin (PLD; Caelyx/Doxil) has been shown to be active against a variety of malignancies with a lower degree of toxicity [22,23]. In a phase II study by Ranson *et al.* [11], PLD achieved a response rate of 31% in patients with metastatic breast cancer and a phase III study by Wigler *et al.* [24] documented the same efficacy of doxorubicin (response rates 27 versus 30%) with a better safety profile, including cardiotoxicity. As preoperative chemotherapy, PLD at the dose of 35 mg/m^2 in combination with cyclophosphamide at 600 mg/m^2 (every 3 weeks, for three cycles) has been tested in 32 locally advanced breast cancer patients with an overall response rate of 73% [25]. Nevertheless, weekly paclitaxel documented high activity in a preoperative setting when combined with anthracycline-based chemotherapy; the report by Green *et al.* [26] showed that paclitaxel given on a weekly schedule was more effective than the same drug given every 3 weeks (pathological complete response on the weekly schedule was 28% compared with 13.7% in patients who received the every 3-week regimen). The efficacy and better safety profile of PLD and weekly paclitaxel stimulated their combination in advanced and preoperative settings. Schwonzen *et al.* [13] achieved an objective response rate of 48% in 21 pretreated metastatic breast cancer patients with a schedule consisting of biweekly PLD at 20 mg/m^2 and weekly paclitaxel at 100 mg/m^2. As neodjuvant treatment, the activity of the PLD/paclitaxel regimen was documented for the first time in a phase II study by Gogas *et al.* [17], with a clinical response rate of 74% and a pathologically complete response of 8% (three patients). On this basis, we decided to start a phase II study with a schedule consisting of biweekly PLD and weekly paclitaxel; the first objective was activity and secondary objectives were safety and percentage of breast-conserving surgery in operable and locally advanced breast cancer patients. To the best of our knowledge, this is the first trial with this schedule in a preoperative setting of breast cancer and the first report of activity in terms of conservative surgery. In our study we obtained 74% of objective responses on breast tumor with 9% of pathological complete response (three patients); in three other patients the disappearance of infiltrating disease was documented. These results are consistent with a number of studies with anthracycline–paclitaxel schedules; the percentage of breast-conserving surgery was encouraging (55%: 15 of 27 operable patients) when compared with results obtained in the Gianni and Romieau trials (65 and 64%, respectively) [27,28]. Regarding the additional benefit of PLD to weekly paclitaxel, we are not able to evaluate its contribution to the clinical and pathological responses: no useful data with PLD in the preoperative setting are evaluable, except for an anecdotal experience of seven patients [29] (28% of response rates with PLD at 50 mg/m^2). In the Gogas study [15], the authors reported the same results in terms of response rates (74%) and pathological complete response (three patients); thus we might conclude that a lower dose of PLD leads to similar results when compared with the standard dose, even though only a direct comparison of the schedules could draw definitive conclusions in terms of efficacy. Toxicity was mild in both studies: grade 3 hand–foot syndrome in four patients (11%) in our trial and in three (9%) in the Gogas trial. After the first five episodes of grade 2–3 hand–foot syndrome, we administered oral pyridoxine 300 mg once a day as prophylactic therapy; this drug does not seem to avoid hand–foot syndrome even though we must take into account the small number of patients and the lack of randomization. Other grade 2–3 nonhematological toxicities (particularly nausea/vomiting, hepatotoxicity, neurotoxicity, arthralgia/myalgia) were rare in both studies; however, grade 2–3 stomatitis was reported in 19% of patients in our study and grade 3–4 neutropenia was higher in the Gogas trial (15 versus 9%). No useful comparison can be made in terms of conservative surgery because of mastectomy performed in all patients after preoperative chemotherapy in the Gogas study. No episode of symptomatic cardiac dysfunction was documented during neoadjuvant and adjuvant treatment. The authors think that lower cardiotoxicity of PLD should be a major issue in the neoadjuvant setting, given the impressive results with trastuzumab in HER-2-positive patients [30]. Moreover, combinations of PLD/trastuzumab and PLD/paclitaxel/trastuzumab have already been tested in metastatic breast cancer patients [31,32]. In the Chia trial, 52% of objective

response rates were achieved with PLD/trastuzumab; 10% of patients reported cardiotoxicity (based on an the absolute decline in LEVF of more than 15% in the asymptomatic state, regardless of the absolute value). In the Karabelis study, the response rates were 71% with the PLD/paclitaxel/trastuzumab regimen; neither significant ejection fraction decline nor symptomatic cardiac event was observed. Therefore, we may hypothesize combining our schedule with trastuzumab to increase pathological complete response with a better safety profile. In summary, this study documented that a schedule with a low dose of PLD every 2 weeks and weekly paclitaxel is active in terms of objective response and conservative surgery in operable and locally advanced breast cancer. Toxicity was manageable even though hand–foot syndrome remains a peculiar side effect in spite of a lower PLD dose.

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